EXHIBIT B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1 CASES**	**Master File No. 2:12-MD-02327** **MDL No. 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

PROLIFT POLYPROPYLENE MESH – GENERAL ANALYSIS AND PATHOLOGY

Prepared By:

Stephen M. Factor, M.D., FCAP, FACC
Professor of Pathology & Medicine

I. BACKGROUND AND QUALIFICATIONS

I am an anatomical pathologist, and Chairman of the Department of Pathology at Jacobi Medical Center (JMC) and North Central Bronx Hospital (NCB) which are two of the 11 Heath & Hospital facilities in New York City. Jacobi (where pathology from both JMC and NCB is performed) is the major trauma receiving hospital for Bronx County, which has a population of 1.5 million people. I perform surgical pathology and cytopathology on a daily basis, and review virtually all of our autopsies, with my attending staff. Our department examines over 12,000 surgical pathology cases, 12,000 gynecologic and non-gynecologic cytopathology cases, and 40-50 autopsies yearly. We have a very large number of gynecologic specimens from both of our hospitals. I graduated with honors from the Albert Einstein College of Medicine (AECOM), and then I trained for 2 years in General Surgery at the University of Michigan where I assisted in and performed surgical procedures. I returned to AECOM where I trained in Anatomic & Clinical Pathology (interrupted by 2 years in the United States Army Medical Corps where I worked as an anatomic pathologist), completing my training in 1975. Since 1975 I have been on the full-time faculty of Albert Einstein College of Medicine (which is immediately across the campus from Jacobi Medical Center) where I currently am a tenured Professor of Pathology & Medicine (Division of Cardiology). I am Board Certified in Anatomic and Clinical Pathology. I am a Fellow of the American College of Pathology (FCAP) and the American College of Cardiology (FACC). I was named a Distinguished Alumnus of Albert Einstein in 1998 (at that time one of 19 out of 8000 graduates since 1959). I was a founder of the Society for Cardiovascular Pathology, and I served as President in 1988-1989. I was the founding Editor-in-Chief of the Society's journal, Cardiovascular Pathology, which is the only journal in the field; I was Editor-in-Chief for 10 years. I have been honored nationally and internationally.

My grant-funded research and the majority of my publications have dealt with virtually all aspects of cardiovascular disease. I have lectured nationally and internationally in the field of cardiovascular pathology at invited meetings and symposia. Among my studies, I have dealt with tissue injury and wound healing. I have researched connective tissue in the heart (collagen Types I, III, and IV) both pathological as well as physiological (i.e. interstitial matrix) with a focus on structure-function relationships. I have studied the effects of collagen breakdown (i.e. collagenase activation) and tissue remodeling. I have done extensive published research on the effects of diabetes mellitus and systemic hypertension on tissue and blood vessels. I have published studies and performed unpublished investigations with one of the leading international figures in wound healing, Dr. Stanley M. Levenson, a distinguished faculty member of Albert Einstein, and an attending surgeon at Jacobi Medical Center (the Burn Center at JMC– one of only 2 in New York City- is named in his honor and memory). I have studied bio-prosthetic materials (bovine pericardium and porcine aortic valves) in animals and humans. I have

evaluated mechanical and bio- prosthetic valves, and foreign materials including Dacron and ePTFE (Gore-Tex). I have studied mesh materials including polypropylene primarily in hernia repair. I am familiar, as part of my surgical pathology practice, with pathological changes associated with polypropylene sutures, as well as other materials used for sutures. I have studied hundreds of cases of vascular and valvular procedures with polypropylene and Prolene sutures. I have studied multinucleated giant cells and their association with foreign bodies by light microscopy and electron microscopy. Finally, in the course of this litigation I have studied approximately 20 cases of gynecologic mesh.

My opinions that follow are held to a reasonable degree of medical and scientific certainty. Attached to this report are my *curriculum vitae* (Ex. A), which sets out my education and training in detail and lists my publications; a list of the materials I reviewed for this case and materials/exhibits which I will use to support my opinions (Ex. B which among other things includes photographs, photomicrographs, and pathology slides I have reviewed); my fee schedule (Ex. C); a list of deposition and trial testimony in the last 4 years (Ex. D).; and figures (Ex. E). I expect to review the deposition transcripts of certain of plaintiffs' experts in this case, and I may develop further opinions after having done so.

II. INFLAMMATORY RESPONSE AND FOREIGN BODY RESPONSE WITH IMPLANT

A. Wound healing: Acute and Chronic Inflammation

All wounds of epidermis or mucosal-lined tissue (i.e. vagina, bladder, rectum, pelvic floor, etc.), regardless of whether they are surgical or accidental, heal with a relatively uniform pattern that is consistent from patient to patient. Healing is essentially similar between individuals, and between most mammalian species used in laboratory studies. Although there may be some variability in timing, pathologists take this into account when they provide short ranges for various aspects of the healing response (i.e. acute inflammatory response in the first 1-2 days; granulation tissue beginning at approximately 4-7 days, etc.).

Once a wound is produced, even if hemostasis is adequate, there will be some degree of blood oozing from traumatized micro-vessels (capillaries, venules, arterioles) into the wound space. The blood includes the red cell component, white blood cells, platelets, and plasma. Red blood cells are relatively inert; they undergo hemolysis over several days releasing hemoglobin into the immediate surroundings that is broken-down by inflammatory cells (see below) into non-degradable iron (hemosiderin). The latter is a golden-brown pigment that is phagocytosed by macrophages; or if too large for phagocytosis, it is deposited into the tissues (most often within stromal collagen). Hemosiderin is a marker of surgical hemorrhage, but it and/or red blood cells are not direct components of the body's wound healing response.

The initial events (1) following in the first few hours after a wound is produced include platelets that normally circulate in blood. Platelets are anucleated cellular fragments of

megakaryocytes in the bone marrow that contain prostaglandins, histamines, serotonin; adenosine diphosphate (ADP), the metabolite of the high-energy intracellular phosphate (ATP) needed for cellular function, is present and it activates platelets and causes them to swell and become "sticky". Together with the vasoconstricting platelet prostaglandin thromboxane (TxA2) and ADP, platelets clump in the wound site (a similar process occurs in disrupted blood vessels). Thrombin from the clotting cascade interacts with TxA2 to convert soluble fibrinogen in the plasma to fibrin, which is a fibrillar protein that together with platelets sticks to the cut edges of a wound leading to tissue adherence and hemostasis. Fibrin acts as a biologic mesh within the wound, ultimately leading to a "scab" which helps to maintain the apposition of the wound edges. The wound space in the fibrous stroma (or submucosa) fills with aggregated fibrin and blood; extension to the surface mucosa occurs if the mucosal lining also was incised.

Beginning shortly after wound production, but peaking within the first 12-24 hours, polymorphonuclear neutrophils (PMNs) from blood are attracted by the endogenous or exogenous release of chemoattractants including leukotrienes and cytokines. The neutrophils have multiple lysosomal proteolytic and collagenolytic enzymes that degrade any necrotic debris, including cellular material or collagen fragments. Within 1-2 days after initiating breakdown of devitalized tissues the PMNs undergo auto-destruction with nuclear fragmentation (karyorrhexis) that peaks at about day 3, and is completed by day 4. Concurrent with the neutrophil breakdown, circulating monocytes reach the site through the bloodstream, and are transformed into macrophages. Macrophages are scavengers that phagocytose debris, and prepare the site for the onset of healing and ultimate scar formation.

It is worthwhile to point out that other cells participate in the healing process including those with vasoactive properties or responders to anaphylaxis (mast cells); those that can damage tissues or organisms such as parasites, or respond to an allergen (eosinophils); and those that participate in the immune response, either cell-mediated (lymphocytes) or antibody-mediated (plasma cells). Different proportions of cells occur in different scenarios depending on whether the wound is sterile or infected, and is in a controlled surgical environment versus traumatically induced. For a sterile surgical wound, the important cellular components are the neutrophils, followed by the macrophages, and then granulation tissue. The following will describe the granulation tissue response.

Granulation tissue is composed of endothelial cells, and myofibroblasts (cells that have a dual function of contractility leading to wound contracture, and synthesis of connective tissue proteins). Beginning at approximately 4 days, endothelial cells form buds that lead to new blood vessels (neo-vasculogenesis). These new capillaries are maximal within the first week (4-7 days). Beginning at around the same time, myofibroblasts secrete type III collagen or reticulin that serves as a biologic mesh at the wound site. Starting in the 2nd week and then continuing for many months, fibroblasts secrete soluble type I collagen which

polymerizes into insoluble fibrils and larger fibers, and with increasing cross-linkage develops more mature fibrous tissue. Type I collagen ultimately becomes mature scar, a process that takes up to 3-6 months to complete. Maturation occurs with a progressive decrease in vascular supply, so that mature scar at 6 months is relatively acellular with widely separated larger blood vessels, and a microcirculation that is difficult to appreciate by light microscopy. Once mature, at 3-6 months, collagen may alter its composition to a certain extent by a decrease in water content, or by binding glycoproteins non-enzymatically in patients who are diabetic (see below). Local tissue ischemia from multiple etiologies including cigarette smoking may also affect the extent of type I collagen cross-linking, and may decrease its tensile strength. Other glycoproteins such as those of myxedema in hypothyroidism may affect the composition and strength of collagen. Relative vitamin deficiency (vitamin C) and copper deficiency also may affect mature collagen, since vitamin C and copper are necessary for collagen type I cross-linkage.

B. Acute versus Chronic Inflammatory Cells

The discussion above described the temporal development of scar tissue that occurs over 6 months before maturation of collagen. The entire process is dependent on the interaction of multiple different cell types including inflammatory cells, and cells that play a structural role by synthesizing protein (myofibroblasts) or that lead to the development of blood vessels (endothelial cells). The terminology for acute and chronic inflammation is partially dependent on this temporal progression: neutrophils (PMNs) are recognized as acute inflammatory cells and they predominate in wound healing in the first 3-4 days of the process; whereas in contrast, monocytes which become macrophages, are considered to be chronic inflammatory cells, yet they are present as early as 4 days following wound onset which is still the acute phase of the healing process. The cellular composition of inflammation is more complex than that related to the time in which the cells appear in the wound (2).

1. Lymphocytes:

Lymphocytes, approximately the same size as red blood cells, occur as two main types: B-cells and T-cells. The cells have numerous functions which are too complex to describe in this overview. The type of lymphocyte can only be identified routinely in tissue by immunohistochemistry. They are classified as chronic inflammatory cells, but they may be present at the onset of an inflammatory reaction; thus temporal chronicity is not sufficient to describe their presence. Their function in a cellular process or in wound healing also may not be evident from morphology alone. Suffice to say, lymphocytes are virtually always present in wound healing and scar development with or without foreign materials such as mesh. Their presence within scar tissue is not an indication of an infection or an adverse response; it is a recognized component of reparative collagen. They are also routinely present in normal tissues, often in sites associated with an interface between the external

and internal environment such as the vagina (as well as nasopharynx, oropharynx, tracheobronchial tree, and gastrointestinal tract, among others). Pathologists are trained to recognize whether the presence of lymphocytes is abnormal, based on a knowledge of normal histology, a recognition of the extent of the cellular response, and a determination of whether the cells are limited passively to tissue stroma or are participating in a degradative or injurious process.

2. Plasma Cells:

Plasma cells are secretory cells that secrete immunoglobulins in response to antigens. They are normal components of tissues throughout the body, often in association with lymphocytes (i.e. spleen, tonsils, lymph nodes). They participate in response to injury, and they may be found as a component of chronic inflammation in response to wound healing.

3. Eosinophils:

Eosinophils are granulocytes that are primary inflammatory cells associated with allergy (i.e. bronchial asthma), but they also have a cytotoxic function in response to parasites. They contain a neurotoxin in their granules, and they have other chemicals that serve as anti-inflammatory agents (i.e. histaminase). Of note, they are often found together with lymphocytes, monocytes, plasma cells and macrophages in chronic inflammatory responses (in the lower esophagus, they are markers of gastric acid reflux). Less commonly, they participate in acute inflammatory processes where ordinarily neutrophils would be the major cellular response. Thus, in relatively infrequent cases of acute appendicitis or acute cholecystitis, for unknown reasons, the eosinophil may be predominant. Eosinophils are not a common feature in response to the implantation of polypropylene meshes, including Prolene Soft.

4. Mast Cells:

Mast cells circulate in the blood as basophils, but when they exit the blood vessels and are found in tissue they are known as mast cells. They also (along with neutrophils and eosinophils) are classified as granulocytes due to multiple cytoplasmic granules. In isolation, they can be recognized with routine hematotoxylin and eosin staining of tissue; however, when they are within an area of pronounced inflammation, they generally require special stains to identify the cytoplasmic granules (which stain metachromatically [purple], rather than red or blue). Like lymphocytes, they may also be a normal component of tissue, and their presence does not necessarily imply a pathological disease state. They play a vasoactive role by releasing histamine that contracts smooth muscle in blood vessels (and in other tissues), leading to increased vascular permeability. They activate platelets and they also release heparin, thus playing a role in inflammatory responses. At the far end of the inflammatory spectrum, they are major participants in anaphylaxis.

5. Monocytes and Macrophages:

Monocytes are circulating mononuclear cells, slightly larger than lymphocytes, released from bone marrow. Once in the blood stream they can circulate for up to a mean 1-3 days (half-life of 1 day) before they exit capillaries and migrate through tissue. When "activated" by cytokines and adhesion molecules secreted by lymphocytes and other inflammatory cells, they transform into macrophages (or histiocytes, used synonymously) by increasing their cell size and their content of lysosomal enzymes. They have as their primary function phagocytosis of biologic materials including tumor cells, damaged tissues, necrotic debris (i.e. lipid from adipose tissue, or cholesterol in atherosclerotic plaques), antibody-coated cells (i.e. red blood cells leading to the residual hemosiderin iron pigment described above); or in response to foreign materials. The foreign body response is distinct, if the macrophages cannot phagocytose the material (see below). Comparable to lymphocytes, plasma cells, and mast cells, macrophages may be normal residents of connective tissue stroma. Once they have phagocytosed small materials like lipid (and become "foamy" macrophages), or particulate material such as hemosiderin, they may persist in the tissue for many months or years, even after the tissues have completely healed.

With small particulate material such as bacteria or necrotic debris, the macrophage phagocytoses the inciting agent (i.e. internalizes it in endosomes at the cell membrane that fuse with lysosomes), that lead to bacterial killing or digestion of the necrotic debris. Once the irritant is eliminated, then the macrophage eventually disappears. This is different from situations where large foreign bodies such as polypropylene fibers cannot be phagocytosed by macrophages, or fused macrophages that become foreign-body giant cells (phagocytosis is precluded by the size of the inciting agent). The initiation of the process of attraction and activation of monocytes to the site is similar to what occurs with small organisms or materials; however, since phagocytosis cannot occur with large foreign bodies, there is apposition of the macrophage and/or giant cell to the surface of the foreign body, with no specific initiation of an ongoing inflammatory or immune response. Once surrounded by multinucleated foreign-body giant cells, the process is **static and stable**. The giant cells persist in the tissue around the fibers in this state for years. There is no evidence that there is a continuous and persistent secretion of enzymes into the space around the apposed giant cell and the polypropylene foreign body (see next paragraph for further discussion).

6. Multinucleated Giant Cells:

Multinucleated giant cells (MNGC) are derived from the cytoplasmic fusion of tissue macrophages. They are participants in granulomatous inflammation (along with macrophages, lymphocytes, and fibroblasts), in response to infectious (i.e. tuberculosis or fungus, etc.), or non-infectious etiologies (i.e. Crohn disease or sarcoidosis, etc.). They can degrade or destroy infectious agents through their release of hydrolytic enzymes, products of oxidative metabolism, and chemoattractant cytokines that modulate other inflammatory

cells. This is not a continuous process; even for biologic materials there are anti-inflammatory agents that limit or halt the inflammatory response.

When MNGC respond to biologic or exogenous foreign material they are known as **foreign-body giant cells**. In general, the foreign materials they respond to are too large to be phagocytosed by endocytosis into the cytoplasm where they can be attacked by lysosomal proteolytic enzymes. When the foreign materials, either natural (i.e. hair shaft) or exogenous (i.e. suture or mesh), are too large to be engulfed, the MNGC surrounds the foreign material by cytoplasmic filopodia-like processes that isolate the material from the surrounding environment. This is a natural biologic response that does not imply an adverse response. The foreign-body MNGC with its surrounding material may persist for years in an unchanged and **inactive state** (see above). This is somewhat different from MNGCs in granulomata, where when the infectious agent is killed, or the immunologic stimulus for granuloma is controlled or eliminated by immunotherapy, the granuloma and its MNGCs heal by fibrous scarring, often with loss of the MNGC. For most large foreign bodies, there may be no granulomatous inflammation associated with the foreign body, but only a MNGC response.

7. Acute on Chronic Inflammation:

The discussion above has focused on the natural cellular components of inflammation and wound healing, as temporal events, and a process where there may be involvement of chronic inflammation early in healing. However, inflammation and/or wound healing is not always linear and uni-directional. Superimposed events can alter the "normal" inflammatory response. Thus a "healed" fibrous scar underlying a mucosal surface may be altered if the mucosa ulcerates or erodes into the collagenized stroma. When this occurs, the tissues may revert to the initial stages of a wound with neutrophils predominating, especially if the tissue is infected. Persistence of the infection may lead to "chronic" neutrophilic inflammation well beyond the normal 1-4 day phase of neutrophils, together with a more chronic response comprising lymphocytes and macrophages. The erosions that may provoke the acute inflammatory response and which may lead to tissue damage, may result from factors other than those related to foreign body (i.e. mesh placement); thinning of postmenopausal vaginal mucosa, trauma from intercourse, and systemic factors such as smoking, diabetes mellitus, and ischemia may all play a role. Vaginal mucosal erosions also may occur in the absence of mesh due to: radiation and chemotherapy for gynecologic cancers, following use of pessaries, treatment of vaginal condylomata and dysplasia with lasers or cautery, childbirth, and vaginal infections, among others.

Any surgical site, whether with or without mesh, can become infected by bacteria which may affect the wound healing response, or may damage the already healed surgical site. Large pore monofilament mesh, because of its pore size, may allow for the ingress of inflammatory cells that can clear or limit infection (see below). This has been studied in

patients, and macroporous polypropylene was shown to have increased resistance to infection compared to other meshes (3, 4).

C. Tissue Integration with Mesh:

The wound healing and the cellular inflammatory responses described above in surgically incised tissues are comparable to the response when a biologically inert mesh is employed as a matrix. The matrix provides artificial support and tensile strength for the tissues until the body's own healing takes place over 3-6 months when mature collagen is sufficient to support the tissues. Prior to 3-6 months without mesh, the tissue support is dependent on surgical apposition of incised edges, and sutures. Breakdown of tissue, and/or loss of suture support by pulling free from the suture site, and lack of tensile support probably accounts for the much higher rates of recurrence between surgical colporrhaphy versus the use of polypropylene mesh in prolapse repair (5-8). The success rates in the latter mesh groups were significantly better than non-mesh colporrhaphy in multiple studies (87% versus 55%; 91% versus 72%; 81% versus 65.6%; 87% versus 59%).

Prolene and Prolene Soft are considered Type I macroporous meshes, which allow for entry of macrophages, fibroblasts, blood vessels and collagen fibers into the pores (9). The tissue response shown with Prolene Soft and Prolene meshes in published literature demonstrates this concept, with appropriate ingrowth of tissue and mild inflammatory reaction (10-12). Others have considered pore size <1mm as small pore, and large pore mesh with pore size >1mm (13). Regardless of the definition, large pore polypropylene meshes such as Prolene Soft and Prolene allow for the entry of inflammatory cells comprising the wound healing response described above, including the myofibroblasts and endothelial cells of granulation tissue. Thus fibrous tissue is deposited within the pores between the woven mesh fibers ultimately contributing to the tensile strength of the composite collagen and mesh structure. Small pore size also can affect the response to any bacteria that may gain access to the mesh with the small pores allowing ingress of bacteria, but limiting the ability of inflammatory cells to react to the infection. The ultimate example are meshes made of ePTFE (Gore-Tex) which have pores less than 10 um, used for vascular grafts (where obviously, the small pores size prevents leakage). These grafts typically have a dense fibrous layer on the outer surface months after implantation, with no fibroblastic ingrowth or infiltrating inflammatory cells. If the graft becomes infected, bacteria can penetrate the micropores, but inflammatory cells cannot gain access.

There is no discrete scar encapsulation of the large pore polypropylene mesh. The mesh is not integrated into the tissue through growth of collagen around the mesh, since the granulation tissue characteristic of wound healing can enter the large pores and lay down initially collagen type III, and subsequently collagen type I. Accordingly, the collagen between the pores separating the knitted polypropylene fibers provides support for the repair where it was previously lacking. Evidence for the adequacy of collagen integration

and differences in inflammatory responses of large pore polypropylene (Prolene and Prolene Soft) mesh has been described in experimental comparisons in animal models (14, 15) and in human subjects (10, 11, 16). The tissue integration was best with polypropylene mesh with a relatively mild inflammatory response (17,18).

In my own observations, it is difficult to appreciate a border between the embedded mesh and collagen and the surrounding vaginal stroma. There is no plane, anatomic or virtual, where one can separate the mesh with fibrous tissue between the pores from the adjacent tissues. The scar tissue that is present around and between the mesh fibers is a normal response to surgery and the implantation of foreign material. It is only "bridging" in the sense that the mesh is integrated into the stroma, as it is designed to do. It is not sharply delimited from the fibrous tissue in the vaginal stroma, as it would be if there was "scar plate" formation, as alleged by certain experts for the Plaintiffs. In fact, other than its presence around the mesh, it is often very difficult to identify a scar from the surrounding vaginal stroma. It is not like skin where scar tissue leads to thinning of the overlying epidermis, and loss of the normal skin appendages in the dermis. There also is no biologic or scientific evidence of which I am aware that scar around mesh is "harder" than the "soft and supple" collagen that has been claimed by at least one Plaintiff's expert (see below). It is also important to realize that wound healing has a component of individual variability which cannot be anticipated or prevented. Abnormal hypertrophic (non-keloidal) scars frequently result from surgical wound healing which can occur anywhere surgical incision through collagenous stroma leads to wound healing; on the skin these hypertrophic scars often require plastic surgery repair. The development of hypertrophic scars appears to be an idiosyncratic response to injury. In contrast, keloid scars in African-Americans are genetically programmed and they are abnormally hard; but they are typically limited to the skin, not other sites such as the vagina or peri-urethral tissues.

In summary, the term bridging fibrosis (or fibrotic bridging) appears to be a subjective description of the normal collagen deposition around and between mesh fibers. There is no fibrous capsule around the mesh that can be removed separately from the mesh and from the surrounding tissues, similar to the capsule around breast implants. In contrast, there is a smooth transition between the fibrosis around the mesh and the adjacent stroma. Any attempt to separate this fibrous response is subjective, biased and unreliable.

D. Factors Affecting Wound Healing With or Without Mesh:

There are many factors including behavioral, genetic, and idiosyncratic that impact the wound healing response. Prominent examples of these factors are described below:

1. Diabetes Mellitus:

Diabetes mellitus is a complex metabolic and endocrine disorder that has systemic effects, including an impact on collagen metabolism and wound healing. Since most women affected by prolapse and incontinence are middle-aged or postmenopausal, they are in the highest risk group for development of Type 2 diabetes mellitus. Diabetes thus may affect the success of repair whether or not mesh is employed. The role which diabetes mellitus plays is multifactorial.

Diabetes has effects on large vessels by enhancing the development and severity of atherosclerosis. Although there may be a component of tissue hypoxia and/or ischemia secondary to large vessel atherosclerosis and stenosis, most of the effect of diabetes on wound healing is through its impact on the microvasculature. Endothelial cells are affected by hyperglycemia, leading to endothelial dysfunction and microcirculatory hypoxemia. This is a direct result of alterations in the reactivity of micro-vessels; as well as due to the development of thickening of peri-capillary basement membranes (19,20**).** The thickened basement membranes arise from increased glycoprotein bound to Type IV collagen that is the major component of capillary basal lamina (see below). The thickened basement membranes decrease capillary permeability for oxygen thereby leading to relative micro-environment ischemia. The capillaries also are "leaky" and they cause microscopic edema. The combination of decreased tissue oxygenation and leakage of fluid into the peri-capillary space may potentially interfere with wound healing.

There is also a passive metabolic consequence of diabetes mellitus and hyperglcemia: non-enzymatic glycosylation of proteins and tissues. Hyperglycemia leads to passive binding of **advanced glycosylation end-products (known as AGEs)** to protein. This occurs with red blood cell hemoglobin, and it affects the release of oxygen from the hemoglobin at the capillary level contributing to local ischemia (the glycosylation of hemoglobin also is the biochemical basis for the measurement of hemoglobin A1c, which provides a snapshot of glucose levels over the approximately 3 month life span of red blood cells). Non-enzymatic glycosylation also affects the cross-linkage and maturation of Type I collagen. The combination of local tissue ischemia and dysfunctional collagen cross-linking may lead to direct and indirect effects on wound healing, and/or maintenance of scar tissue integrity.

Lastly, diabetes mellitus also affects tissue susceptibility to infection, the frequency of infection with organisms that may not be pathogenic to non-diabetics, and the ability of the patient's inflammatory response to control or prevent infection. Acute inflammatory cells (PMNs) in an environment of hyperglycemia are less capable of killing bacteria; conversely, many bacterial and fungal organisms thrive in a high glucose milieu.

Finally, although it is not directly related to diabetes mellitus, another endocrine disorder, hypothyroidism may have very similar effects on collagen synthesis and maintenance as diabetes. Hypothyroidism may affect the micro-environment with changes in capillaries,

deposition of myxoid glycoprotein in tissues (i.e. myxedema), and through its effects on cardiac function, tissue perfusion.

2. **Smoking:**

Cigarette smoking, in addition to its injurious effects on the lung which may over years lead to decreased oxygen and increased carbon dioxide systemically, has immediate and persistent effects on tissues throughout the body, including collagen. Similar to diabetes mellitus, there may be damage to large vessels by enhancing the development of atherosclerosis leading to potential ischemia in tissues supplied by stenotic vessels. This vascular injury is mediated by the effects of nicotine and other adverse chemicals in smoke on endothelial cells, and smooth muscle vascular walls. Nicotine also has potentially profound effects on the micro-environments producing vascular spasm and endothelial injury at the microcirculatory level. Cigarette smokers also have increased circulating carbon monoxide levels due to preferential binding to hemoglobin compared to oxygen, and which reduces the capacity of erythrocytes to release oxygen at the tissue level; this is another cause of local tissue ischemia in smokers.

Nicotine is a vasoconstrictor, and even in the absence of anatomic damage (i.e. atherosclerotic plaques) to muscular arteries, both large and small, it can induce spasm of the smooth muscle, and lead to endothelial dysfunction. Both are progenitors of the development of atherosclerosis, but even without permanent injury to the artery wall, episodes of vascular spasm can lead to tissue injury. Similarly, the microcirculation is affected since both arterioles down to the pre-capillary level, and post-capillary venules have contractile capability (21). Even capillary endothelial cells may contract somewhat through actin filaments in their cytoplasm, but the main effect of cigarette smoke on the capillary is through damage to the endothelium [capillaries are composed of a single layer of endothelial cells surrounded by a basal lamina or basement membrane]. Thus, throughout the body, all tissues supplied by capillaries for a distance of 25-50 um, which is the distance that oxygen can passively diffuse along a gradient outside of the vessel (22) can be affected if the capillary does not function normally. Obviously, this does not lead to overt necrosis of the micro-environment, but it can affect the health of the tissues, in regard to healing, inflammatory response to injury, and protein synthesis.

Cigarette smoking has direct effects on collagen synthesis, and maintenance of mature collagen. This can be appreciated simply by the enhanced skin wrinkling often seen in chronic smokers. Wrinkling is a manifestation of collagen degeneration, and slowing of collagen repair. In sites distant from the skin, wound healing may be impeded by decreased and/or inefficient collagen synthesis, and type I collagen cross-linking to produce mature scar. Thus, with mesh placement, the integration of the collagen into the mesh may be impacted, and the repair may be weaker than it should be leading to surgical failure and prolapse recurrence.

3. Hypertension:

Hypertension does not have direct effects on collagen and wound healing comparable to diabetes mellitus and cigarette smoking, but it can act together with either to enhance their adverse impact. Upwards of 70% of diabetic patients are also hypertensive, and together they lead to worse pathophysiological effects on the microcirculation, than either condition alone (Factor). Similarly, there can be a synergistic effect of smoking and hypertension on both large and small blood vessels, enhancing potential tissue ischemia. Hypertension, in particular, is associated with vascular sclerosis of small muscular arteries. Vascular sclerosis is the deposition of collagen in the vessel wall, together with smooth muscle proliferation, leading to luminal stenosis, and decreased blood flow distal to the arteries.

4. Nutrition:

Although overt starvation is not an issue in western countries (other than rare cases of anorexia nervosa), relative deficiencies of nutrients may occur inadvertently, or purposefully, in dieting. The wound healing response with adequate collagen synthesis leading to mature scar tissue is dependent on sufficient dietary protein to provide the amino acids required. Decreased protein intake may occur through dieting, or through dietary fads, and may have an unanticipated adverse effect on wound sites. This is not an insignificant issue in society where obesity has become an epidemic in children and adults. There is also the potential that excess weight may have on loss of tissue integrity leading to increased hernias and organ prolapse.

As briefly noted above, other dietary deficiencies such as vitamin C and copper, insufficient to produce overt disease such as scurvy, may still have an effect on collagen synthesis. Both are required for collagen cross-linking. Full-blown vitamin C deficiency leading to scurvy is essentially a connective tissue disease due to the fragility of blood vessels and tissue throughout the body. Similarly, other than rare genetic abnormalities of copper metabolism, copper deficiency when it is produced in experimental animals, may lead to ruptured blood vessels due to insufficient and weakly crosslinked collagen.

E. Factors Affecting Pain With or Without Mesh:

The above sections have dealt with wound healing, inflammation, infection, incorporation of mesh into tissue, and potential patient-specific adverse conditions that can affect all of these elements of prolapse repair. However, a prominent allegation in this litigation that affects patient welfare and surgical success is the patient's appreciation of pain sensation. The pathologist may have a limited role to play in evaluation of the tissues where the pain may be generated. The reasons for the limited role are as follows:

There is no way for any pathologist, simply by observing tissue histologically, to predict whether a patient is experiencing pain, except in very limited circumstance not typically present in mesh specimens or in *ex vivo* tissue. Likewise, abnormalities of nerve fibers- perceived or real- cannot predict pain. Pain is a subjective sensation, and ability to experience it is variable from patient to patient; it also is dependent on other factors including neuropathies (such as diabetes mellitus, renal failure with uremia, liver failure, central nervous system conditions, etc.), as well as certain types of inflammation, not the chronic inflammation seen in explanted mesh (see below). It is not possible to observe myelinated nerve fibers in tissue and morphologically determine whether they are pain fibers, pressure fibers, or even non-functional fibers. Any surgical disruption of the vaginal wall (whether with or without mesh placement) can potentially injure nerve fibers or lead to their presence in scar tissue. This is a natural phenomenon. Inflammation directly of nerves (i.e. neuritis) may cause pain; but again, there is no way to identify the fibers affected as specifically pain fibers. Moreover, there are disease of nerves involving marked inflammation (including granulomata) that lead to a loss of sensation rather than pain (i.e. leprosy). Traumatic neuromas (Morton's neuroma) can be painful; traumatic neuromas are usually associated with inflammation which is present in the fibrous tissue that is associated with the proliferation of the neural outgrowths. Again, other traumatic neuromas can result in the loss of function rather than pain, depending on the type of nerve involved in the neuroma.

In my experience, there are small nerves distributed throughout the vaginal tissue, most often with no evidence of degeneration, disruption, or inflammation within the actual nerve. Neuromata are rare. It is possible that inflammatory mediators of pain are released locally and stimulate pain fibers, but this cannot be determined by tissue examination. The increased inflammation in those cases associated with the erosions may be a competent explanation for the pain. The lack of association of inflammation with pain has been noted by several investigators (17, 23). In the Hill study (23), there was less inflammation in the tissues excised for pain compared to those patients who had mesh excised for voiding dysfunction which would argue that inflammation was not directly involved. Klosterhaffen (17) noted no correlation between inflammation and removal of mesh for pain, and also observed that inflammation decreased with the time the mesh was in place. Both investigators commented on the persistence of MNGC around the mesh fibers, which by itself is not an indicator of pain, or adverse response to the foreign material.

As a result, there is no scientifically reliable way to correlate pain with the findings seen in histology. As discussed above, efforts to do so looking at inflammation and fibrosis have been unavailing, and instead highlighted the inability to do so.

F. Summary and Conclusions:

The above sections have focused on the normal biologic response to wound healing whether mesh is used or not. It has described the inflammatory cells, the development of

granulation tissue, the production of collagen, and the time course of these events. The wound healing in sites requiring support during and after the surgery is enhanced by the use of macroporous Prolene Soft mesh, which allows for the ingrowth of connective tissue in between the pores, maintenance or enhancement of tensile strength, and maintenance of 3-dimensional elasticity. The inflammatory response associated with Prolene Soft is generally mild and is not essentially different than what would be expected if no mesh was employed. The one difference between repair with and without mesh is that the inflammation with mesh is composed of chronic inflammatory cells including multinucleated giant cells (MNGC). It should be noted, however, that all foreign bodies (including biologic materials) elicit a MNGC response, which by itself is not evidence of an adverse event or condition.

The report also discussed the role that acute events, superimposed on chronically implanted healed mesh, has on the tissues: specifically the development of erosions or tissue ulcerations on the underlying vaginal wall and the mesh itself. Secondary acute inflammation can occur. There are many reasons for potential erosion including smoking (25), or others discussed above in this report beyond the scope of this summary, but it is noteworthy that the large pore size allows for enhanced ability of inflammatory cells to combat infection if bacteria gain access to the mesh from mucosal erosion.

Multiple other conditions were discussed that have an impact on mesh implantation and healing. These include the most significant metabolic effects of diabetes mellitus and cigarette smoking on wound healing, collagen synthesis, and tissue oxygenation. Other less common conditions were also addressed, which in individuals may still play a major role. Finally, pain was addressed, primarily in regard to the lack of direct role that pathological analysis may play in its assessment; but also in regard to a direct lack of association between pain and inflammation, which in any case is relatively less in Prolene Soft mesh compared to other materials.

G. General Critique of Plaintiffs' Pathology Expert Dr. Vladimir Iakovlev's Opinions and Contentions:

In his Expert Report that relates to all WAVE I cases, Dr. Iakovlev makes a number of assertions that are not supportable by biologic and scientific principles. Scientific analysis requires comparison of affected subjects matched with an otherwise similar control population without alterations, in order to draw conclusions regarding cause and effect. Simply illustrating examples of tissue damage, degree and type of inflammation associated with that damage, and alterations of the tissues (including nerves and blood vessels) only is meaningful if matched control subjects with mesh implants do not have those changes. In addition, none of the symptomatic subjects that Dr. Iakovlev describes are even matched internally for age, co-morbidities (i.e. diabetes mellitus, hypertension, smoking history,

obesity, hypothyroidism, collagen-vascular disease, psychiatric disease, etc.), type of prolapse requiring surgery (uterine, cystocele, rectocele), post-surgical time until complications, sexual history, delivery history, and experience of the surgeon implanting the mesh. He simply provides illustrated examples based on his analysis of affected plaintiffs in this litigation, and then expands his observations to the entire population of patients who have received polypropylene mesh implants.

His basic contention highlighted in his report on page 13, is:

"The mesh acts as a foreign object and the body attempts to degrade and isolate the mesh. The mesh itself, as a foreign object, and the body reaction to the mesh damage the tissues in a critical anatomic location. This damage occurs in all patients, however, to a variable degree. The manifestations range from subclinical to fully developed complications triggering mesh excision".

This scientifically unproven contention essentially extrapolates Dr. Iakovlev's findings from a selected small group of patients who have undergone mesh excision for various complications, to the entire population of patients with successful mesh implants. This is a classic example of a biased and non-controlled study in which selected adverse findings are used to draw conclusions about patients with mesh who have not been analyzed. To suggest that every patient with mesh has damage induced by the mesh itself and the body's reaction to the mesh is pure speculation since these patients and their tissues cannot be studied. This is not science, but pseudoscience.

Specific analyses follow:

1. **Multinucleated Foreign-body Giant Cells:**

It is accepted that polypropylene mesh will elicit a foreign-body giant cell reaction comparable to all foreign bodies. Foreign bodies attract macrophages which maintain their cellular structure or fuse to become multinucleated cells. The macrophage or multinucleated giant cell will either phagocytose the material if it is sufficiently small (i.e. silica crystals or anthracotic pigment), or surround it with cytoplasmic extensions (filopodia) if it is large like polypropylene fibers or sutures. In addition, identical macrophages or multinucleated giant cells react to **natural** materials in the body that are not "foreign", but are either altered (i.e. antibody-coated or distorted/fragmented erythrocytes; necrotic fat; cholesterol crystals in atherosclerotic plaques), or are in an abnormal location (i.e. hair shafts in a pilonidal cyst/sinus or in a cystic teratoma (see Figure 1, Factor); keratin debris from a ruptured epidermal inclusion cyst). The materials are not degraded or destroyed, but remain intact for years. Dr. Iakovlev has proposed that the primary function of the multinucleated foreign-body giant cell (along with its progenitor cell the macrophage) is to degrade the polypropylene fibers by undefined environmental stress and oxidation presumably from enzymatic activity of inflammatory cells. There are a number of observations, even in Dr. Iakovlev's own illustrations that would suggest that this is not

true, or even if partially true it plays no role in tissue pathology, patient symptomatology, or mesh dysfunction.

For one thing, multinucleated foreign-body giant cells have a variable distribution in tissue around mesh fibers and within the fibrous tissue surrounding mesh. It is noteworthy that when Dr. Iakovlev illustrates significant foreign-body inflammatory reaction he selects a few examples and illustrates them at high magnification (20X and 40X; see pages 21-23 of Figure set 1, and page 24 of Figure set 2a). Yet many low magnification illustrations in his report show fibers or fiber spaces with few if any multinucleated foreign-body giant cells (see pages 48-50, Figure sets 6d, 7a-b; page 63, Figure set 9b). These are only several illustrations from his own work which belies his conclusions. The fact is that many fibers do not have foreign-body giant cells; or if they do they are not circumferential around the entire fiber (see Figure 2, Factor.)

In addition, there is an intrinsic bias in tissue examination that affects many pathologists: the tissues being examined are 3-dimensional structures that are sectioned and evaluated in 2-dimensions (generally less than 4-5 microns thick). Observing a multinucleated foreign-body giant cell (or a macrophage) around a polypropylene fiber seen in cross-section in a histological section does not inform the examiner whether the fiber has multinucleated foreign-body giant cells above or below the plane of section. So not only do multinucleated foreign-body giant cells not surround all polypropylene mesh fibers, they also do not surround them circumferentially in most cases, and they do not invest the fiber with their cell processes along the entire 3-dimensional length of the fiber. Yet Dr. Iakovlev has stated that "environmental stress and oxidative degradation **facilitated by macrophages** [emphasis added] have been found to be the most likely mechanisms to explain *in vivo* degradation of polypropylene [page 8 of his report]."

Dr. Iakovlev has stated that enzymatic fiber degradation caused by release of enzymes from macrophages and multinucleated giant cells, also leads to cytotoxic tissue damage in the immediate surrounding environment. If this was true, then it would be anticipated that around fibers associated with macrophages and multinucleated giant cells there would be an exuberant inflammatory response and obvious tissue necrosis, which is not seen. Tissue necrosis is limited to those cases of vaginal mesh erosion; it is not observed around mesh fibers embedded in fibrous stromal tissue. It does not affect collagen, nerves or blood vessels. In addition, degraded particles of fibers would be small enough to be phagocytosed by macrophages and multinucleated giant cells, and these are not seen either. Dr. Iakovlev also does not explain how this speculative and unproven cytotoxicity of degraded products, or even any evidence whatsoever of cytoxicity, does not adversely affect the much larger population of patients who have had successful mesh implants for prolapse or hernia repair.

Fiber degradation will be discussed below.

2. Fiber Degradation:

There is no question that implanted polypropylene mesh fibers, or polypropylene sutures, develop an outer coat of material that Dr. Iakovlev describes as "bark" because it also shows cracking perpendicular to the long-axis of the fiber. The cracking is very regular in spacing, almost verging on periodicity. Dr. Iakovlev suggests that this outer layer is a degradation of the fiber. This conclusion, as well as others dealing with the adverse consequences of this surface alteration of the fiber, is pure speculation. The composition of the surface material is unknown. It is sometimes bi-refringent similar to the polypropylene, but it also weakly stains with PAS which suggests a glycoprotein component (see Figures 3-4, Factor). Some of the bi-refringence is reflective from the adjacent fiber, but the material is independently bi-refringent when it is separate from the fiber (see Figure 4, Factor). There are a number of observations that suggest that the outer layer, whether composed of polypropylene or not, does not play any role in mesh pathology. It has only become of interest to the Plaintiff's because of earlier statements from Ethicon that polypropylene did not degrade.

a. As noted above, PAS (periodic acid Schiff) stains glycoprotein, and in many examples of the outer coating, there is weak PAS staining of the material suggesting the presence of glycoprotein (see Figure 2, Factor). This may suggest a process similar to the Splendore-Hoeppli phenomen associated with a protein coating around the surface of organisms such as Actinomyces sulfur granules or certain parasites when they invade tissues, or foreign material (i.e. barium, see Figure 5, Factor). Other proteins may be present, as well that do not stain with PAS and are not bi-refringent. This includes fibrin and pro-collagen, among others. Commonly, Dacron fibers used for prosthetic valve sewing rings and surgical patches have a coating of eosinophilic fibrin or collagen around each of the fibers (see Figure 6, Factor).
b. When fibers are separated from the outer "bark" coating by the histological microtome knife that often leave fiber spaces (typically filled-in by Dr. Iakovlev by computer yellow coloring of the empty spaces), the fiber surface can be examined along with the "bark" surface left behind. Both surfaces are smooth, with the fibers being convex, and the "bark" being concave (see Figure 4, Factor). This clean surface is not characteristic of an enzymatic or oxidative degradation process. Rather, with tissue degradation there is irregularity of the surface. In fact, osteoclasts, which are derived from the same monocytes as macrophages and multinucleated giant cells, when they remodel bone the interface between the osteoclast and the bone surface shows prominent irregularities, often resembling "rat-bites", typically seen in osteomyelitis.

c. If the development of "bark" was due to an ongoing enzymatic and/or oxidative process, I would anticipate that the process would continue unabated, until the fiber was destroyed with time. This might be particularly evident with very thin polypropylene sutures (7-0 or 8-0) used for vascular anastomoses. Yet, this does not happen (see Figures 7-8, Factor). In fact, Dr. Iakovlev shows in his graph on page 97 of his report that with only 21 data points (presumably patients), the "bark" thickness plateaus after 5 years. Of note, he does not show the comparable negative change in

the fiber diameter; if the "bark" is 5 microns thick at 5 years, then the fiber should have decreased in diameter circumferentially by 10 microns if it was being degraded to produce the outer coating. Fibers with an outer coating do not appear thinner, nor are they different from adjacent fibers without a "bark" layer.

d. The encasement of the fiber up to 5 years or longer, suggests that the fiber is unreactive comparable to the protection afforded by pre-rusted structural steel used in external environments such as bridges and roadways susceptible to oxidation and rusting. If the coating was a continuous process due to the release of enzymes and/or oxidative free radicals, then why should the degradative process be self-limited? A 5 micron thick outer coat should not be a hindrance to continued release of macrophage or multinucleated giant cell enzymatic activity on the polypropylene fiber surface. Oxygen molecules themselves can passively diffuse through tissue including basement membrane containing collagen type IV, and interstitial collagen containing collagen type III and type I, for up to 50 microns. One would assume that oxygen free radicals and enzymes (i.e. myeloperoxidase which releases oxygen free radicals) from macrophages could diffuse for an even greater distance.

e. If the "bark" encasement of fibers contains degraded polypropylene as claimed by Dr. Iakovlev (Figure set 13, pages 84-95), as highlighted by the incorporation of blue dye granules in the "bark" and the comparable bi-refringence of the "bark" with polarized light, then how can he explain why the same enzymatic activity that allegedly caused the degradation, did not degrade the same material in the "bark"? In fact, the multinucleated foreign-body giant cell is external to the outer "bark" layer, and immediately in contact with it, and not the fiber surface; yet the surface of the "bark" externally, and internally where it is in contact with the polypropylene fiber, is smooth (see Figure 4, Factor). Enzymatic degradation is not likely to dissolve material smoothly, but it is more likely to lead to irregularities of the surface similar to what is seen with bone remodeling. This occurs because the enzyme-containing intracellular lysosomes are not uniformly distributed along the macrophage membrane. The lysosomes release their enzymes after fusing with the macrophage cell-membrane, and in those locations the enzyme concentration is highest. Thus, if Dr. Iakovlev is correct, then the surfaces of the polypropylene fibers, as well as the inner and outer surfaces of the "bark," should not be smooth but should be pitted or irregular. Even his illustrations, as well as my observations, do not support a pitted surface for the fibers or the "bark".

f. The claim that degraded fibers lose their tensile strength and become brittle is also pure speculation. Dr. Iakovlev cites one paper for this assertion (his reference 448) which describes the effects of sunlight and UV light on polypropylene, which is irrelevant for *in vivo* implantation. If surgeons were concerned about the brittleness of polypropylene sutures and their loss of tensile strength due to degradation, they would not continue to use them in critical sites where failure could result in catastrophe and patient death (i.e. suturing of coronary artery grafts to native arteries; prosthetic valve implantation with

suturing between the Dacron valve ring and the native annulus; and suturing of aortotomy sites or aortic vascular grafts).

g. Finally, in regard to integration of mesh and collagen scar (see below), the tensile strength of the supporting tissue used in pelvic prolapse repair is initially dependent on the support provided by the polypropylene mesh during the period when wound healing and collagen maturation is taking place. However, by 3-6 months the type I collagen has matured and has reached its maximum tensile strength by one year. The tensile strength of the mesh is important only during the period in which the collagen has not reached maturity. Functionally, the support of the pelvic tissues is dependent on the collagen, but since the collagen and the mesh are so integrated they act together. Any, even minimal loss of tensile strength of the polypropylene is irrelevant at that point.

3. Mesh Integration and Distortion:

Dr. Iakovlev describes fibrosis in and around large pore polypropylene mesh as a unique and presumably abnormal process that leads to complications; however, the growth and maturation of collagen is comparable to wound healing without mesh, except that the mesh provides tissue support and serves to direct the collagen fiber growth in 3-dimensions, until the collagen matures. Illustrated and suggested abnormalities of this process by Dr. Iakovlev and others overlooks the obvious fact that they are studying examples of mesh explanted from patients with problems following surgery as well as numerous co-morbidities that can affect the success or failure of the surgical repair. As previously noted Dr. Iakovlev is dealing with a selected, uncontrolled group that cannot be generalized to the entire population who received mesh implants without complications. Additionally, he uses his imagination to reconstruct the 3-dimensional mesh-fibrosis organization based on 2-dimensional images (see below).

The large pore polypropylene mesh is designed to allow for ingrowth of collagen between and around the fibers thereby integrating the mesh-collagen composite into the native tissues, while at the same time providing support until the collagen matures. The contraction and remodeling of the collagen takes place whether mesh is present or not; maturation of scars of the epidermis can be observed and followed over time by anyone. Similarly, native tissue repairs without mesh (i.e. colporrhaphy) will also undergo healing, maturation, and remodeling; however, because the support of the tissues is dependent on already potentially abnormal connective tissue without any external support provided by mesh, this explains the high rates of failure and recurrence of this type of procedure. The concept that there is a unique form of scarring known as scar plate is pointed out by Plaintiffs' experts as an adverse consequence of using mesh. The development of so-called scar plate simply represents the ingrowth of the collagen around the fibers. The distinction of where this scar plate is located and how it is separate from the surrounding tissues is

often purely arbitrary. There is no surgical plane that can be identified. The scar associated with the mesh often blends imperceptibly with the surrounding fibrous tissue (i.e. vaginal submucosal stroma). Placing scar labels and arrows on illustrations as Dr. Iakovlev does on a unique example of mesh and fibrous tissue surrounded by fat (see his Figure set 2, pages 24-30) cannot be used to generalize the integration with mesh and collagen with fibrous stroma. If scarring associated with mesh was separated from the surrounding tissues, then surgeons could use this plane to completely remove the mesh when complications arise. In fact, in most situations, the mesh-collagen composite is integrated in the tissue, and only portions of mesh and fibrous tissue can be removed. When the mesh and scar is surrounded by adipose tissue as in Dr. Iakovlev's example, then complete removal is facilitated.

Also, in discussing mesh distortion, curling and folding, Dr. Iakovlev not only takes a 3-dimensional process seen in 2-dimensions, but he arbitrarily "connects the dots" by using his computer color program and then drawing computer lines where he believes the tissue has been distorted (see his Figure sets 10 and 11, pages 65-75). Drawing straight or curling lines (see 10c and 10d) is innovative but provides no real information.

4. Pain:

Pain with and without mesh was discussed earlier in this report. It is worth repeating however, that any surgical intervention has the potential to injure pre-existent nerves. It is impossible by morphology alone to determine whether nerves are pain fibers, motor fibers, or pressure fibers. When Dr. Iakovlev (partially based on his own study) states that "nerve involvement has been reported to exceed 60% for meshes excised for reasons of pain", this is a classic example of a selected and biased analysis of tissues studied with no control. He also implicates chronic inflammation associated with mesh "...which creates the background capable to lower the pain sensitivity threshold." This completely unsupported statement also is contradicted by the work of Hill and Klosterhaffen (17,23, cited earlier in this report) in which there was less inflammation in the tissues excised for pain in the Hill study compared to the mesh excision for voiding dysfunction; whereas, Klosterhaffen found no correlation between inflammation and the removal of mesh for pain. How variable numbers and distributions of multinucleated foreign-body giant cells with mesh implantation can contribute to pain, Dr. Iakovlev does not inform us. Presumably, since it is a virtual certainty that all implanted mesh has multinucleated giant cells intimately associated with it, then by using Dr. Iakovlev's reasoning all patients with mesh should experience pain. This is not the case.

Illustrating isolated examples of nerves and ganglia (see Figure 9, Factor), either directly affected by mesh fibers or in the general proximity of mesh fibers, does not prove that the cause of pain (if it was even present) was due to that specific injury. The nerves and ganglia illustrated in his report (Figures set 3 and 4, pages 31-44) have unknown function. The illustration of nerve twigs in the vaginal mucosa (page 44) is meaningless, since the vaginal mucosa always has nerve twigs whether there is mesh or not. True nerve injury, with the

development of a traumatic neuroma may be painful if formed from damaged pain fibers; however, traumatic neuromata can occur with surgical incision alone and no mesh.

5. Vascular Alterations:

Dr. Iakovlev makes the statement on page 17 of his report that: "Mesh placement is associated with vascular damage, where both the larger vessels and the smaller capillaries become affected. Tissue affected by insufficient blood supply can undergo necrosis and/or fibrosis (scarring)." The same can be said for surgical intervention without mesh, so to attribute this potential "injury" to mesh is hyperbole. In addition, his statement and accompanying illustrations (Figure set 9, pages 62-64), fail to take into account that the pelvic tissues are highly vascularized, and rarely are susceptible to ischemia or inadequate blood flow that leads to tissue necrosis (i.e. in situations of congestive heart failure, due to ventricular dysfunction or shock). Secondly, the pelvic vessels undergo post-menopausal changes leading to vascular sclerosis (i.e. fibromuscular mural thickening, hyalinosis, and luminal narrowing), which are completely natural changes and have nothing to do with mesh (see Figure10, Factor). Thirdly, the changes of "obliterated artery" and "damaged artery" illustrated by Dr. Iakovlev on pages 62-63 are sectioning artifacts (particularly the obliterated vessel on page 62 which has a telescoped lumen). Fourthly, Dr. Iakovlev does not inform us whether the illustrated vessels were from patient(s) with hypertension, diabetes mellitus, history of tobacco use, or hypothyroidism, any one of which or several together could have caused the vessel changes. Lastly, the "thrombosed capillaries" on page 64, if they are truly thrombosed and not just congested, would have to be affected by hyperacute thrombosis almost certainly induced by the surgical procedure to remove the mesh.

6. Summary:

Dr. Iakovlev makes a number of unsupported statements and draws conclusions based on his selected observations of mesh specimens from patients who have had complications. He then extrapolates these selected data to the much larger population of patients with mesh who have no complaints or complications. He does not provide any control data, nor can he since he has no access to mesh from these successful implants. He also does not stratify his selected patients by age; presence of co-morbidities that can affect inflammation, wound healing, pain, vascular alterations; or absence of co-morbidities. He implies or states that the inflammation that develops in response to the mesh, particularly the macrophages and multinucleated foreign-body giant cells, plays an adverse role in the development of mesh pathology. This does not take into account the variability of this inflammation and the fact that only rare fibers are surrounded by multinucleated cells circumferentially or along their length. He focuses on polypropylene degradation with no knowledge of the composition of the surrounding "bark". He does not explain how the surface layer develops without ultimately destroying the fiber or even narrowing it. He claims that the alleged degradation leads to a loss of tensile strength and brittleness of the mesh with no evidence; statements contravened by successful implantations of soft large pore mesh, as well as longstanding

utilization of polypropylene suture in critical locations without catastrophic loss of support. He makes unsupported statements about the development of pain and vascular damage, without taking into consideration all of the multiple interactions both local and systemically that impact the etiology of these pathologies.

In summary, much of what Dr. Iakovlev presents is pseudo-science which cannot be used to draw valid and scientifically meaningful conclusions about Ethicon polypropylene mesh.

All of the findings and statements in this report have been expressed within a reasonable degree of medical certainty. I reserve the right to supplement this report if additional information becomes available.

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Stephen M. Factor, M.D.

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